REMARKS

Rejection of Claims and Traversal Thereof

In the January 28, 2003 Office Action,

claims 1-11 and 13-15 were rejected under 35 U.S.C. §112, first paragraph.

This rejection is hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. § 112, first paragraph

In the January 28, 2003 Office Action, claims 1-11 and 13-15 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

According to the Office, the disclosure fails to provide adequate guidance in a number of areas. As such, applicants will address each of the Office's remarks and contentions individually.

1. Initially, applicants must clarify to the Office that the presently claimed invention is not related to gene therapy and the AAV-2 virus is not used as a vector to transfer foreign genes. When the Office completely reviews the present claims and specification, it will be evident that there is **NO** discussion relating to gene therapy. The presently claimed invention uses the AAV-2 virus as an infectious agent that is **administered in combination with chemotherapeutic agents**. It must be recognized that the AAV-2 virus is not used as a vector that has a chemotherapeutic agent inserted in the viral genome nor is there any foreign gene inserted into the genome of the virus. Applicants request that the Office specifically point out claims in the present application reciting methods of gene therapy or sections in the specification wherein there is any discussion that would constitute a method of gene delivery of a foreign gene package.

2. According to the Office:

> "Although the specification teaches administering AAV2 at 10^9 -10^{10} particle/kg body weight intravenously, intratumorally, orally or cutaneously, it does not provide support that these method of delivery can overcome the technical difficulties that existed in the art and achieve successfully therapy in human subjects. The example provided by the specification only teaches intratumoral injection to deliver AAV2 virus. **Therefore, the claimed method is at most enabled for intratumoral delivery of AAV-2 virus.**"(emphasis added)

Applicants vigorously disagree because the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, and the specification need not disclose what is well known in the art. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984). Further it has been consistently held by the courts that the first paragraph of 35 USC §112 requires nothing more than objective enablement. In satisfying the enablement requirement, an application need not teach, and preferably omits**, that which is well known in the art**. Further, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC §112, first paragraph as stated by the Board in *Staehelin v. Secher*, 24 USPQ2d 1513 (B.P.A.I. 1992) citing *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962) "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be."

The Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker,* 24 USPQ2d 1443 (Fed. Cir. 1992). The Office has not met this burden, especially regarding transmission of the AAV-2 virus, because it has been well known since about 1960 that the AAV-2 virus is highly transmissible and it is speculated that almost 80 % of the human population show signs of previous infection. Obviously, transmission and/or introduction of this AAV-2 virus to such a high number of humans was not by intratumoral injection. As such, introduction of the virus is not limited to intratumoral, in fact, it is known that there are multiple modes of easy transmission including routes through the mouth, eyes, inhalation, subcutaneously, intravenously and the like. As a matter of fact, because of the infectious nature of this virus, great care is exhibited by laboratory technicians when handling of the virus in a laboratory setting because of its multiple modes of introduction. Thus, one skilled in the art would certainly recognize that the virus can be introduced to a mammal's system by multiple modes including: orally, subcutaneously, in combination with intravenous chemotherapy treatment, or intratumorally. Further, it is recognized by skilled artisans that the virus is capable of infecting a wide range of cells and can integrate into the genome of the infected cell to establish a latent

infection. The Office cannot dispute this information which is available to most undergraduate students enrolled in a virology class.

Further, it is well known that tumor cells are highly profused and this mode of systemic transmission of the virus provides an easy route for introduction of the virus into the tumor cells. The results shown in the present application provide proof that AAV-2 infected tumor cells, especially chemotherapeutically resistant cells, responded favorably in the presence of the AAV-2 virus. In light of that which is known to skilled artisans regarding transmission and cellular acceptance of AAV-2 virus in addition to present specification which contains a description of the claimed invention, the Office has not provided any convincing reasons why one of ordinary skill in the art would not consider the description sufficient and enabling. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996).

3. Applicants submitted a Declaration on December 13, 2002, which discussed and showed that AAV-2 has tumor-suppressive activity and can sensitize freshly explanted human tumor tissues to γ irradiation and to various chemotherapeutic agents *in vivo*. Also, it was shown that infection with AAV-2 enhanced the cytotoxic effect of 5-FU on pancreatic tumor cells and reduced tumor growth in immunocompetent Lewis rats challenged with syngeneic pancreatic cancer cells. Further, the test results showed that rats infected with the AAV-2 virus and treated with chemotherapeutic drugs remained in better physical condition compared to controls treated with only chemotherapy.

According to the Office:

> "Applicants disclose the sensitization of a implanted pancreas tumor in an immunocompetent rat model to chemotherapeutic agent 5-FU. Applicants demonstrated that intratumoral AAV-2 administration prior to treatment with 5-FU significantly reduced tumor growth compared to 5-FU treatment alone. Applicants further disclose that the chemotherapy-related toxic effects are reduced in the animals with concomitant AAV-2 administration. **However, Applicants do not disclose whether these tumor cells are resistant to chemotherapy or radiotherapy.** This is an important piece of information that is necessary to support the enablement of the claimed method because the method is drawn to a method for lowering chemotherapy or radiotherapy induced resistance by infecting patients with AAV-2. Therefore, the declaration does not support the enablement of the claimed method." (emphasis added)

In the enclosed Supplemental Declaration (Appendix A) Dr. Von-Knebel-Doeberitz describes the specific reasons for selecting pancreatic cancer cells to test the presently claimed invention. As stated in the Declaration, pancreatic cancer cells were known to be notoriously resistant to cancer treatment including chemotherapy and radiotherapy, and thus, using these types of cells provided the definitive testing model to show the effectiveness of the claimed combination therapy of infecting with AAV-2 and administering a chemotherapeutic agent. Clearly if the combination therapy was found effective in pancreatic cancer cells, it is certainly effective in less drug resistant cancer tumor cells. The results of the multiple testing procedures already of record in the prosecution of the present application show that applicants' claimed invention is effective in chemotherapeutically resistant cells. Further these results support the enablement of the claimed invention. Accordingly, applicants respectfully request that all 35 U.S.C. §112, first paragraph rejections be withdrawn.

Petition for Extension of Time/Fees Payable

The applicants hereby petition for a two (2) month extension of time, extending the deadline for responding to the January 28, 2003 Office Action from April 28, 2003 to June 28, 2003. The entry of this petition results in a petition fee of $205.00. A check in the amount of $205.00 is submitted herewith in payment of the petition fee for a two month extension. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

CONCLUSION

The pending claims 1-4, 6-11 and 13-15, as now amended, meet all disclosure requirements and patentably distinguish over the prior art, and in view of the forgoing remarks, it is respectfully requested that all rejections be withdrawn, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Qian is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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5) (Previously amended) The method according to any of claims 1-4, wherein the AAV-2 is administered intravenously, cutaneously, orally or intratumorally.

6) (Currently amended) The method according to any of claims 1 to 5, wherein the infecting with the AAV-2 is made before, after or simultaneously with a chemotherapy treatment ~~or radiotherapy~~.

7) (Currently amended) A pharmaceutical composition containing a chemotherapeutic agent and an effective dose of AAV-2 to reverse chemotherapy-induced resistance in patients suffering from a cancer selected from the group consisting of ~~to be treated by chemotherapy is a~~ colon cancer, pancreatic carcinoma, brain tumor and small cell lung carcinoma.

8) (Previously amended) The pharmaceutical composition according to claim 7, wherein the chemotherapeutic agent is selected from the group consisting of: cisplatin, etoposide and cisplatin/etoposide.

9) (Previously amended) The pharmaceutical composition according to claim 7 or 8, wherein the composition is formulated in a member selected from the group consisting of; an injection solution, infusion solution, an aerosol spray or an ointment.

10) (Currently amended) A method for reducing resistance to a chemotherapeutic agent ~~reversing chemotherapy-induced resistance~~ in a patient suffering from a chemotherapy drug resistant ~~small cell lung carcinoma~~ cancer and ~~previously~~ treated for the cancer by a chemotherapeutic agent selected from the group consisting of cisplatin, etoposide and cisplatin/etoposide, the method comprising:

infecting the patient with a sufficient amount of AAV-2 to reduce resistance ~~to reverse the chemotherapy-induced resistance~~ to the chemotherapeutic agent, in combination with administering the chemotherapeutic agent to the patient; and

determining if the ~~chemotherapy-induced~~ resistance to the chemotherapeutic agent is reduced. ~~reversed.~~

11) (Previously added) The method according to claim 10, wherein the AAV-2 is administered at a dose of 10^9 - 10^{10} AAV particles/kg body weight.

12) Previously cancelled

13) (Currently amended) A method for enhancing chemosensitivity of cancer tumor cells to ~~reversing chemotherapy-induced resistance in a cancer cell previously treated for the cancer by~~ a chemotherapeutic agent to reduce tumor growth, the method comprising:

infecting the cancer cells with a sufficient amount of AAV-2 to enhance chemosensitivity of the cancer tumor cells ~~reverse the chemotherapy-induced resistance~~ to the chemotherapeutic agent, in combination with administering the chemotherapeutic agent to the cancer cells, and

determining if tumor growth is reduced. ~~the chemotherapy-induced resistance to the chemotherapeutic agent is reversed.~~

14) (Previously added) The method according to claim 13, wherein the chemotherapeutic agent comprises an agent selected from the group consisting of: cisplatin, etoposide and cisplatin/etoposide.

15). (Previously added) The method according to any of claims 14, wherein the cancer cell is a colon cancer cell, pancreatic carcinoma cell, brain tumor cell or small cell lung carcinoma cell.

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